Remarks

Claims 1-10 and 23-32 are pending in the present application. Applicants note with appreciation the Office's acknowledgment of Applicant's entitlement to the priority date of the United Kingdom application filed June 28, 1999.

The rejections of claims 1-12 on grounds of lack of sufficient written description, indefiniteness and anticipation by Toth et al. have been withdrawn. The Information Disclosure Statement filed June 20, 2006 has been considered and the Sequence Listing previously filed has been canceled from the application.

The Office is objecting to the amendments to the specification on June 20, 2007 and November 3, 2006 as introducing new matter to the disclosure which is not supported. The stated reason is that the scope of the disclosure is "changed" by removing sequence data, thus constituting new matter. The amendments to the specification made November 3, 2006 added commas between letters in the left column of tables on pages 17, 18, 21 and 23. Applicants are amending these same tables herein to remove the commas with the intention of restoring the tables to their original content as filed. All previous amendments to these tables having been effectively canceled, and the tables now being the same as when originally filed, no issue of new matter can remain with respect to the tables.

The amendments made to the specification on June 20, 2006 included deletion of the sequence listing (which was filed not as part of the original application), and also deleted sequence identifier information from the tables (which also had been added

subsequent to the filing of the original application disclosures). These amendments therefore cannot add new matter since they deleted only matter which was not part of the original application. For these reasons, the new matter rejection should be withdrawn.

In addition, Applicants would like to point out that the original application, as filed, contained no peptide sequence information and contained no disclosure concerning peptides. Applicants are submitting herewith a Declaration executed by Roger Randal Charles New, the inventor of the present application (hereinafter "New Decl. I"). In this declaration, Dr. New states that the application as drafted does not contain any peptide sequence information and that the application does not refer to sequences in the tables affected by these amendments. See New Decl. I, paragraph 5. Therefore, removing any added material related to sequences from the application is not addition of new matter.

Furthermore, as the New Decl. I states, a person reading the application as a whole, with the tables, in context, would immediately understand that the letters in the left column of the tables refer not to peptide sequences (which are nowhere discussed in the application), but to the identity of head groups of the conjugates present in particular conjugate mixtures. The letters are nowhere identified as sequences. See New Decl. I, paragraph 6. In referring to the letters denoting conjugate head groups, the specification clearly refers to "individual conjugates," for example on pages 21 and 24, as stated in the New Decl. I, paragraph 6. Particularly in the tables, where the left column lists the one-letter codes for the amino acid head group of each conjugate, the area immediately to the right lists those

same conjugates with those same head groups as being dispensed, matching the letters in the left column. See New Decl. I, paragraph 6.

Therefore, the one-letter codes listed together do not refer to peptides at all, but to individual conjugates with different amino acid head groups. See New Decl. I, paragraph 7.

Applicant submits that the objections to the specification are improper. No sequence information was present in the original application, therefore removal of any of such later-added material cannot add new matter. Skilled persons reading the application as a whole would immediately recognize this. Applicant requests, therefore that the Examiner consider the New Decl. I and the content of the original application, and withdraw these objections.

Claims 1-12 are rejected as anticipated by Crabtree et al., WO 95/02684 A1 (hereinafter "Crabtree"). This reference is cited as disclosing chimeric proteins that have a binding domain fused to an action-domain and that may dimerize to a ligand and also may contain a transmembrane region for insertion in a membrane. Applicants would like to point out that the claims recite amino acid and peptide head groups, but not "protein" head groups or proteins.

Applicants are amending the claims herein to cancel claim 1 and amend dependent claims to change dependency to claim 32, which is not rejected here and therefore is considered novel over Crabtree. Claims 11-12 were canceled in a previous amendment. All claims under examination now incorporate the features of claim 32. Applicant submits that this rejection has been overcome and requests that the Office withdraw this rejection.

Applicants also would like to point out that the claims now recite "[a]n isolated micelle," as discussed with respect to this rejection in the Office Action, page 6, second paragraph. The claims are novel over Crabtree for this additional reason, since Crabtree only discloses cells that express the chimeric proteins.

Claims 1-12 are rejected as anticipated by Capon et al., WO 96/23881 A1 (hereinafter "Capon"). This reference is cited as disclosing chimeric receptor proteins which are an association of conjugates which would inherently include acidic and basic amino acids. These acidic and basic amino acids are asserted to read on the head group claim in claim 1. The reference also is cited as teaching transmembrane domains which would inherently form a hydrophobic aggregation, allowing the asserted head groups to position to form epitopes.

Applicant has amended the claims as discussed above. The claims now contain the features of claim 32, which is not rejected here and therefore is considered novel over Capon. Applicant submits that this amendment overcomes the rejection of claims 1-10 as anticipated by Capon and requests its withdrawal. The amended claims also are novel over Capon for the additional reason that Capon does not teach isolated micelles, but only cells that express chimeric protein.

Claims 1-6 and 8-12 are rejected as anticipated by Ueda et al., U.S. 2003/0095962 A1 (hereinafter "Ueda"). Ueda is cited as disclosing chimeric polypeptides that have the property of associating with each other in the presence of an antigen. The inherent presence of acidic and basic amino acids in all proteins is cited as evidence that these compositions have a hydrophilic head group as claimed; transmembrane sequences are cited as reading on the claimed hydrophobic tail groups. As discussed

above, Applicant has amended the claims herein such that all claims now recite the feature of claim 32, which is not rejected here and therefore is considered novel with respect to Ueda. Applicant therefore submits that the rejection has been overcome and requests withdrawal of this rejection. As for the references discussed above, the claims are novel over Ueda also because Ueda does not teach isolated micelles.

Applicant refers the Office to the second declaration of Roger Randal Charles New, hereinafter "New Decl. II." In this declaration, Dr. New describes the invention and explains why the invention described and claimed in this application is different structurally and functionally from the compositions described in the prior art cited by the Office against this application. Applicant refers the Office to this declaration concerning some of the statements made in the Office in the context of the anticipation rejection. The present specification clearly explains that the invention claimed here does not encompass large proteins as described in the prior art. See New Decl. II, paragraph 8.

Claim 32 is rejected as obvious over each of Crabtree, Capon and Ueda separately or in view of Onyuksel et al., U.S. Patent No. 6,217,886 B1 (hereinafter "Onyuksel"). The examiner characterizes claim 32 as drawn to a micelle comprising a plurality of conjugate molecules. The primary references are cited again for their disclosures concerning chimeric protein molecules that have charged amino acids and a transmembrane region, which therefore assertedly embue them with the property of being able to form a micelle with a head group and a hydrophobic tail that inherently meet the elements of claim 1. The Office concedes that none of Crabtree, Capon nor Ueda teach

micelles of conjugates. Onyuksel is relied upon for teaching micelle formation from amphipathic compounds. In summary, this rejection is based on the conclusions that (1) the chimeric proteins of the primary references are amphipathic because they contain basic and acidic amino acids and a transmembrane region and (2) because they are amphipathic they inherently form micelles and they meet all of the claim limitations of claim 32.

The Office considers that it would have been obvious for one of skill to make and use a micelle as taught by Onyuksel using the "conjugate" molecules of Crabtree, Capon or Ueda because Onyuksel teaches that micelles have desirable qualities, namely delivery and enhanced bioactivity. Applicant traverses this rejection.

The application reports that conjugates in a micelle, with head groups that are free to move, may interact cooperatively to form an epitope with improved binding. See New Decl. II, paragraph 5 and Figure 2 of the present application. Strong interactions can be achieved even with small head groups compared to conventional biological receptor molecules. See New Decl. II, paragraph 5. Accordingly, these inventive micelles are far less immunogenic than large proteins, and are easier to manufacture, isolate and maintain in stable form. See New Decl. II, paragraph 5.

A skilled person having available Crabtree, Capon or Ueda with Onyuksel would have to modify their teachings significantly to arrive at the micelle claimed in claim 32. See New Decl. II, paragraph 6. First, the chimeric proteins of any of the references would have to be modified to fall within the scope of the conjugates and the head groups of claim 32. See New Decl. II, paragraph 7.

The present application teaches that large proteins are not encompassed by the invention. See New Decl. II, paragraph 8. The claims recite peptides, but do not recite proteins. Proteins are large and give rise to problems such as unwanted immune attack and endopeptidase attack. See New Decl. II, paragraph 8. Therefore a skilled person, reading the claims in the context of the application as a whole as required, would construe the head groups to be any small chemical or biological group but not to include long peptide chains or complete receptors. See New Decl. II, paragraph 8. The inventive head groups as described and as would be understood by a skilled reader, would be small so as to not contain an epitope individually. Epitopes would form only by combinations of head groups. See New Decl. II, paragraph 8.

Crabtree discloses on page 31 that the receptors are at least 50 amino acids. See New Decl. II, paragraph 9. Further, each individual receptor domain in Crabtree contains a complete epitope and can bind to a ligand itself. See New Decl. II, paragraph 9. Therefore the "receptor domain" of Crabtree is not a head group according to this invention. See New Decl. II, paragraph 9.

Capon discloses on page 27 that the proliferation signaling domain (PSD), extracellular clustering domain (ECD), effector function signaling domain (EFSD) and intracellular clustering domain (ICD) are generally about 50-1500 amino acids. See New Decl. II, paragraph 10. Further, each extracellular inducer-responsive clustering domain binds to at least one extracellular inducer molecule. See New Decl. II, paragraph 10. Therefore, the ECD in the Capon chimeric protein is not a head group according to the present invention because it is too large and

each ECD individually contains an epitope. See New Decl. II, paragraph 10.

Ueda discloses variable region sequences V_H and V_L domains. Single domain antibodies consisting of either V_H or V_L typically contain 70 amino acids, so these also are much larger than the head groups of the present invention. See New Decl. II, paragraph 11.

For the same reasons discussed above, a skilled person would construe the term "conjugate" of the present claims to cover head groups of small chemical or biological groups linked to hydrophobic tail groups and not to cover long peptide or protein chains. See New Decl. II, paragraph 12. Therefore, the proteins of Crabtree, Capon and Ueda do not fall within the scope of the conjugates of the present invention. See New Decl. II, paragraph 12.

Because the Crabtree, Capon and Ueda proteins cannot be head groups of claim 32 (i.e. they do not form epitopes by a distinct non-covalent association of head group molecules) there would have been no motivation to place them in a micelle as the Office urges. For example, if one did take the protein of Crabtree, Capon or Ueda and make a micelle containing them, the proteins might be able to move in the micelle somewhat, but they would not form an epitope by distinct non-covalent association of the extramicellar portion. The most that could occur is that multiple proteins would each bind <u>separate</u> epitopes on a single large ligand. This is not the same as <u>creating</u> an epitope by groups of small head groups moving around a single binding site.

Thus, the Capon, Crabtree and Ueda proteins lack at least one of the features of the inventive conjugate molecules and cannot perform the function of joining together to form a single binding site.

In addition, there would have been no motivation to place the chimeric proteins of the primary references in a micelle. The "advantage" cited in the Office Action, of "delivery and enhancing bioactivity of active compounds" is completely irrelevant to the invention here. The conjugates are used in micellular form to allow the head groups to mingle and move together to form aggregations that create an epitope, not to deliver or to enhance the bioactivity of the individual conjugates. The individual conjugates here are not bioreceptors. This asserted motivation therefore is not a proper basis to combine the references. In addition, this purported motivation goes against the teaching of the primary references to express the proteins in a cell. See New Decl. II, paragraph 19.

There is no suggestion in the primary references or in Onyuksel to modify the disclosed large chimeric proteins, each containing its own binding area, to create a small, non-binding head group that when associated with other small, non-binding head groups can create a binding pocket. There is no motivation or incentive for the skilled person to make smaller versions of the Crabtree, Capon or Ueda molecules, which together form a distinct non-covalent association which allows the head groups to position to form an epitope with higher affinity to a ligand than any individual head group. See New Decl. II, paragraph 13.

In the present invention, the conjugate structure allows them to move freely in the micelle so the head groups can associate to form an epitope in the presence of a ligand. The

proteins of Crabtree, Capon or Ueda could not be used to identify the most favorable sequence for binding to a specific receptor because each protein already comprises an epitope that binds to a specific ligand. See New Decl. II, paragraph 13. The Crabtree, Capon and Ueda proteins can only bind a ligand more strongly by binding to more than one epitope on the ligand; they do not together join to form a single, new epitope.

In addition, Onyuksel is concerned with the use of a biologically active amphipathic compound. See New Decl. II, paragraph 14. It does not teach the skilled person to use conjugates according to the present invention where head groups mingle around and form an epitope around a binding site, particularly where the epitope has higher affinity to the ligand than each head group individually. See New Decl. II, paragraph 14. The Crabtree, Capon and Ueda proteins cannot be used in a combinatorial approach to form new, favorable epitopes to identify favorable sequences for binding to a specific receptor. See New Decl. II, paragraph 14. They can only bind according to the epitope they already have.

The proteins of Crabtree, Capon and Ueda are produced by introducing constructs of DNA encoding the proteins into cells. See New Decl. II, paragraph 15. The micelles claimed here are in isolated form, which allows them to be used to identify the most favorable head group combination for binding to a receptor of interest. See New Decl. II, paragraph 15. There is no motivation to attempt this isolation with the Crabtree, Capon or Ueda proteins since the references teach that it is essential for the proteins to be expressed in cells for them to have the desired biological effect. See New Decl. II, paragraph 15.

Another difference between the Crabtree, Capon and Ueda proteins and the inventive conjugates is that they would have to be modified in order to be capable of forcing a micelle. See New Decl. II, paragraph 16. The size ratio of hydrophilic to hydrophobic region in these molecules is so large that steric hindrance will prevent the hydrophilic regions from packing together closely enough to allow the hydrophobic portions to associate adequately. See New Decl. II, paragraph 16. Also, in many cases, both ends of the chimeric protein are hydrophilic, with only a hydrophobic central portion (transmembrane region), which is not a structural configuration conducive to formation of micelles. See New Decl. II, paragraph 16.

As acknowledged by the Office, none of Crabtree, Capon nor Ueda teach micelles of conjugates. Micelles are usually defined as spherical colloidal structures which have a lipidic core and a surface composed of hydrophilic head groups. See New Decl. II, paragraph 17. The cells described in Crabtree do not fit that description. See New Decl. II, paragraph 17. In many cases, the size of each of the individual chimeric protein molecules disclosed by Crabtree, Capon or Ueda can be equivalent in size to an entire micelle. See New Decl. II, paragraph 17. In order to modify these proteins to achieve the outcome claimed herein, one would need to reduce in size and completely redesign the head groups, use different chemical moieties to form the hydrophobic portions, employ different synthetic strategies to form the head groups, and use different chemistry for synthesis and assembly of the constructs, each with distinctly different chemical functionalities in terms of binding. See New Decl. II, paragraph 17. Claim 32 recites that the conjugate molecules <u>form</u> the

micelle, not that they are in a micelle. Applicant submits that the cited chimeric proteins are not capable of forming a micelle.

The peptides attached to the surface of the micelles in Onyuksel also are larger than described in the present invention. See New Decl. II, paragraph 17. Because of their size, structure and method of adherence to the micelles, these peptides do not have sufficient flexibility or freedom of movement to allow adjacent peptides to come together in all possible configurations to enable formation of new epitopes. See New Decl. II, paragraph 17. Therefore, Onyuksel does not provide any guidance as to how or why Crabtree, Capon and/or Ueda should be modified to achieve the objectives of the claimed invention. See New Decl. II, paragraph 17.

A skilled person reading Crabtree, Capon and Ueda in view of Onyuksel would not only be lacking several elements that are claimed in claim 32, but would not have any motivation to modify the teachings in the documents to arrive at a micelle according to claim 32. See New Decl. II, paragraph 18. As well, the skilled person would not even know that this claimed micelle could be achieved, much less how to achieve it or be provided with the tools and guidance needed to do so using the prior art chimeric proteins.

In summary, the teachings of Crabtree, Capon and Ueda not only lack any teachings concerning micelles, they lack any guidance that micelles could be used. The proteins they teach could not form a micelle, in contrary to the Office's unsupported assertion. There is no motivation cited in any of the references Crabtree, Capon, Ueda or Onyuksel which even hint that aggregates of small conjugates in micelle form could be made to freely associate to form a single appropriate binding region for a

ligand. The references only disclose large, specific ligand-binding molecules which can be expressed in a cell, already formed, and bind that specific ligand. With the invention, the epitope only forms by movement of individual elements of the epitope to form the epitope on the ligand. There is no teaching of this conjugate with this type of head group, no motivation to place the proteins of Crabtree, Capon and Ueda in micelles, no ability for them to form micelles themselves, no ability of the proteins to function as the invention does if they were in a micelle, and no reasonable expectation that should those proteins be in a micelle that they would interact to form a new epitope (binding region) other than the pre-selected and pre-constructed epitopes already on the large protein molecules.

Applicant has added new claims 33-34 to the application. Support for these new claims may be found in the specification as a whole and in particular at page 5, line 21, which disclose oligopeptide head groups not exceeding 10 amino acids, and page 6, lines 22-26, which describes conjugates dispersed as a preparation. Page 9, line 25 to page 10, line 2, also describes micelles formed in aqueous medium. The examples, as well, clearly show how an embodiment of the invention was created by dispensing a volume of various conjugates with amino acid head groups and water (see for example page 17, and the text of Example 1). Applicants submit that the new claims, as well as the amendments to the claims are fully supported by written description and do not constitute new matter.

For the reasons discussed above and in the accompanying declarations under 37 C.F.R. § 1.132, Applicant requests reconsideration of the amended application and allowance of the claims.

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